Title: Effects of early postnatal pseudomonas respiratory infection on alveolar remodeling in mice.
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Background: Bronchopulmonary dysplasia is a chronic, disabling lung dysfunction which develops in premature infants in part due to injury of a developing lung. Experimental models of BPD are limited and poorly mimic neonatal clinical exposures. Postnatal respiratory infections in premature neonates are associated with future development of BPD, but this association has not been thoroughly explored experimentally.

Methods: We developed a model of neonatal Pseudomonas aeruginosa pneumonia. 5-day-old C57BL6/J mouse pups were administered P. aeruginosa Pa01 strain intratracheally following ketamine/xylazine anesthesia. Two doses were studied, 1 million CFU (“low-dose”) and 2 million CFU (“high-dose”). Controls received intratracheal injections of PBS (vehicle). Antibiotic therapy with gentamicin was administered for a total 7 days starting at 8 hours post-infection. Bronchoalveolar lavage (BAL) was performed at different time points through an angiocath with 2 instillations of PBS. Lungs were inflated using low-melting agarose and fixed in formalin, sectioned, and H&E stained for morphometric assessment.

Results: At 18 hours post-infection, there was histologic evidence of pneumonia while BAL fluid showed >10-fold elevation in total cell count, mainly neutrophils, and a 15-fold elevation in total protein compared to control mice. Infected mice initially lost weight over 48 then started to recover, though daily weight gain remained 32.5% lower than sham-infected littermates. At day-of-life 15, infected mice displayed histologic evidence of alveolar remodeling with a 67% increase in airspace size by mean chord length and 41% reduction in radial alveolar counts compared to control. This data represents findings with low-dose P. aeruginosa exposure, whereas mice receiving high-dose infection had increased acute lung injury, 30% survival (vs. 90% with low-dose), and worsened alveolar remodeling with the additional finding of pronounced lung interstitial thickening.

Conclusions: Intrapulmonary infection with P. aeruginosa in neonatal mice induces acute lung injury and long-term alveolar remodeling akin to the arrest in alveolar development seen in patients with BPD. This model serves as a platform to further define the immunopathologic mechanisms of BPD.

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